STANFORD UNIVERSITY MEDICAL CENTER

DEPARTMENT OF GENETICS

OCT 31 1977

Dear Dr. Kirschstein:

I am sorry that, as I told you over the phone, I will be unable to appear in person for the hearings on 9 December. Perhaps, nevertheless, I might make a few brief observations by letter.

Clearly there are two motivating orientations for genetic research policy: a) the alleviation of anguish from the afflictions that are clearly labelled as genetic, and

b) clarifying the role of genetic factors in a much wider range of diseases with more complex etiology.

Sickle cell disease is an outstanding example of (a), and competes only with Down's syndrome in presenting a formidable public health problem. The most urgent but surmountable challenge here is the development of practical methods of prenatal diagnosis. The same inquiries in cell- and molecular biology that may make this possible are also likely to open up new therapeutic possibilities, e.g. in the modification of patterns of hemoglobin synthesis to encourage the retention of Hb-F. One cannot ignore also the prospects of euphenic modifications, namely treatments that mitigate the disease without altering the underlying genetic constitution. To target the erythrocytes with minimum risk of other long-term damage will require studies of cell-specificity and of the physiology of the erythrocyte that are still more sophisticated than anything we know or do today.

Fortunately, there are few other monogenic diseases that are prevalent enough to constitute major public health problems in a statistical sense. Studies on these need to be continued, however, with a view to developing methods that will be applicable to the whole range of burdens. There is no way to segregate the knowledge that will provide the key to practical solutions to cystic fibrosis from those for Huntington's chorea! For each of these challenges we need a creative mix of the most fundamental studies of DNA and of cell functions with more clinically oriented investigations and trials. Genetic screening can be justified as cost-effective if applied to the whole battery of afflictions; only in special circumstances against individual rare diseases.

The single-gene diseases are attractive research targets for the more general understanding of the role of genes in human development and pathology. Unfortunately, the most important situations —from a public health and social cost standpoint — are those where genes play an important but shared role. The most evident targets are atherosclerosis, hypertension, schizophrenia, diabetes, kidney stones, and (in some measure) predisposition to some forms of cancer. The role of genetic factors in these diseases is diffuse and poorly understood; but the diseases enumerated count for most of the population's burden of ill health! Particular encouragement should be given to those studies that promise to give us new leverage on these drearily familiar situations.

Paradoxically, it is here that the most fundamental may come closest to the most applied advances. The chief obstacle to the study of polygenic diseases comes, obviously, from the difficulty of assigning a predisposing input to a particular chromosome. New methods of studying DNA, outcomes of 'recombinant-DNA' research with bacteria, offer the most powerful tools for revealing the specificities of single chromosomes and unmasking their role

in the inheritance of these complex conditions. At this stage, aggressive regulatory trends are more serious obstacles than technical hurdles in thwarting the rapid development of these diagnostic tools. I do not believe the public has been properly informed about the risks and costs that it will suffer from the inhibition of research in this field that has already been imposed, and for which there have been grave threats of still more intrusive and bureaucratized controls.

Finally, a word about what genetic research policy cannot, should not and does not address. There has been much fanciful talk about the possibility of genetic modification of people, some of it offered even hopefully with either utopian or medical aims. I have argued elsewhere about the futility of such approaches from a purely technical standpoint — no method of genetic modification could ever be so reliable that it could be applied to people without unacceptable risks of monstrous side-effects. Lest there be any misunderstanding, we should also point out that such efforts are unacceptable social policy: we are hardly wise enough to discard the intrinsic variability and adaptability of our species, and in these circumstances are morally repugnant. Life is full of paradox, and the new one here is that access to prenatal diagnosis and preemptive abortion -- a highly reliable approach to the minimization of genetic disease — makes the development of riskier alternatives at the level of genetic modification ethically impossible.

We cannot lose sight of the fact that the most important penalties of genetic defect are so prevalent — we all carry SEVERAL such genes in every cell — that the idea of eradicating them is utopian. Our purpose in more precise diagnosis will for the most part be directed to better understanding of mechanism, and from that to other preventive and remedial measures.

Sincerely,

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